Remarks

The Office Action mailed January 6, 2009 has been received and reviewed. Claims 1-19, 23, and 31-34 having been canceled, without prejudice, and claims 35-42 having been added, the pending claims are claims 20-22, 24-30, and 35-42. Reconsideration and withdrawal of the rejections are respectfully requested.

Claims 20-22 are amended to recite the subject matter of claim 23.

Claim 29 has been amended to correct the clerical error noted by the Examiner.

The new claims are supported by the specification as filed.

Specification

The specification has been amended at page 15, line 2, to remove the reference to a URL.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 20-23, 26, 27, 29, and 30 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner asserts that the specification

> does not reasonably provide enablement for [a] method of treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a subject having cancer an effective amount of a composition comprising an agent that decreases activity of a MscCa channel, wherein the mechanosensitive channel is a mechanosensitive Ca-permeaable (MscCa) channel wherein the agent is an antibody that specifically binds to an epitope present in SEQ ID NO:6, wherein the cancer is cancer, breast cancer, colon cancer, lung cancer, bladder cancer, ovary cancer, pancreatic cancer, or skin cancer, wherein the antibody decreases activity of the MscCa channel.

This rejection is respectfully traversed.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The information contained in an specification must be sufficient to inform the skilled person how to both make and use the claimed invention.

To begin with, the Examiner refers to three documents regarding the importance of the MscCa channel TRPC1 in cancer. Two of these documents, Gottleib et al. (Eur. J. Physiol., 455:1097-1103, 2008) and Dietrich et al. (Cell Mol. Biol., 455:465-477, 2007) were published after the filing date of the present application. It is improper to use post-filing art to demonstrate a lack of enablement. M.P.E.P. §2154.05(a). This was made clear by the CCPA in *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977), in which the CCPA expressed concern that subsequently generated art could be used to attack patents and thus hinder early disclosure. There are only limited exceptions to this rule, such as the use of post-filing art to demonstrate that one of ordinary skill in the art would not have reasonably believed the prophetic teachings of a specification as of its filing date (*In re Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513 (Fed. Cir. 1993)). Gottleib et al. (2008) and Dietrich et al. (2007) do not include evidence demonstrating that one of ordinary skill in the art would not have reasonably believed the prophetic teachings of the present specification as of its filing date, thus, the Examiner is respectfully requested to exclude Gottleib et al. and Dietrich et al. when considering enablement of the claims.

The third document cited by the Examiner regarding the importance of the MscCa channel TRPC1 in cancer is Verrall et al. (Cancer Letts., 145:79-83, 1999). The Examiner asserts these authors disclose that gadolinium, an inhibitor of the MscCa channel, increases the migration of the prostate cancer cells. There are technical concerns regarding Verrall et al. In particular, it has been shown that the trivalent cation Gd^{3+} is highly chelated by inorganic and organic multivalent anions, such as the anions present

in serum, so that free Gd^{3+} approaches diminishing low concentrations (Caldwell et al., Am. J. Physiol. Cell Physiol. 1998; 275: C619-C621, of record). Verall et al. dissolved Gd^{3+} in medium supplemented with 1% fetal calf serum, a concentration of serum expected to decrease the level of free Gd^{3+} (see also the specification at page 5, lines 8-13). In contrast, the present specification analyzed Gd^{3+} effects in medium without serum present and observed decreased Ca2+ influx and decreased PC-3 cell migration (examples 4 and 5). Thus, the teachings of Verrall et al. showing increased migration of prostate cancer cells are irrelevant when considering enablement of the pending claims.

The specification discloses that a tumor cell's ability to migrate plays a critical role in the spread of prostate cancer, and that identifying a step that promotes the transformation of non-motile to motile tumor cells may provide a therapeutic target for preventing prostate tumor cell spread and metastasis (specification at page 2, line 27 through page 3, line 5; see also Banyard and Zetter, Cancer and Metastasis Reviews, 17, 449-458, 1999, of record). The Examples demonstrate that a mechanosensitive Ca^{2+}-permeable (MscCa) channel is present in tumor cells and that it plays a role in the metastatic activity, e.g., the motility and invasiveness, of such cells. As cell motility is involved in the formation of metastic tumors, treatments that result in an inhibition in the activity of mechanosensitive ion channels are expected to result in the prevention or inhibition of metastatic tumors in a cancer patient.

The specification teaches methods of separately using four different agents (Gd^{3+}, GsMTx-4, anti-TRPC1 antibody, and an siRNA for TRPC1) to decrease activity of a mechanosensitive Ca^{2+}-permeable (MscCa) channel. Examples 5 and 6 show the four agents decreased migration in PC3 cells. Thus, the agents decreased a phenotype known to play a role in the spread of prostate cancer. The PC3 cell line is a human prostate tumor cell derived from a metastatic site, and is recognized by those skilled in the art as a useful cell line for *in vitro* screens to identify agents that may be useful anticancer agents (see, for instance, Danesi et al., Molec. Pharmacol., 47:1106-1111, 1995; Floryk et al., Cancer Research, 64:9049-9056, 2004; and Lee et al., Cancer Metastasis Reviews, 12:21-28, 1993. Moreover, the PC-3 cell line represents actual specific prostate

metastatic tumors; this cell line produces metastatic tumors in mice.

The specification teaches how to identify other agents that decrease activity of a mechanosensitive Ca^{2+}-permeable (MscCa) channel (specification at page 16, line 11 through page 22, line 18). In some aspects the methods include measuring a cell's motility, invasiveness, or the combination thereof. Methods for measuring motility and invasiveness are disclosed as known and routine and may include visualization methods such as time-lapse videomicroscopy or the use of a Boyden chamber.

The specification also teaches how to use agents that decrease activity of a mechanosensitive Ca^{2+}-permeable (MscCa) channel. For example, the specification teaches that agents that decrease activity of a MscCa channel in a cancer decrease motility of the cancer cell, and may be used to treat cancer in a human (specification at page 23, line 29 through page 27, line 20). The specification teaches that such a use may be to treat metastatic cancers originating from various tissues including, for example, carcinomas, sarcomas, leukemias, and lymphomas. Examples include cancers of the prostate, breast, colon, lung, bladder, ovary, pancreas and skin. The specification further provides art recognized methods for administering the agents, including art recognized methods for determining toxicity and therapeutic efficacy (specification at page 28 through page 31, line 12), as well as art recognized methods for formulating a range of doses for use in humans (specification at page 31, line 13 through page 32, line 6).

The applicants teach how to make and use the claimed agents, and submit that the scope of the pending claims is commensurate with the scope of the present specification.

The Examiner asserts that "[i]t is well known that the art of anti-cancer therapy is highly unpredictable," and "prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential." Gura (Science, 273:1041-1042, 1997), cited by the Examiner to show very few compounds are ever found to be useful for chemotherapy, notes in closing that the "future of cancer drug screening is turning almost exclusively toward defining molecular targets" (Gura at the last paragraph). This passage is relevant when considering the enablement of the pending claims, because the applicant has defined mechanosensitive ion channels, for

instance, the MscCa channel, as the target. In other words, the applicants have done precisely what Gura recommends as a potentially "easy way to identify promising cancer drugs."

As pointed out by the Examiner, Zips et al. (in vivo, 19:1-8, 2005) states that prediction based solely on *in vitro* data is not reliable and requires further evaluation in animal tumor systems. However, Zips et al. goes on to state that "the most important function of *in vitro* experiments is to select promising candidates for further testing (Zips et al., page 3 col. 2, last paragraph). Zips et al. also states that "well-established *in vitro* and *in vivo* methods are available for experimental evaluation of new anticancer agents" (page 6, col. 1., last paragraph). Thus, despite the earler teachings of Freshey (1983) and Dermer (1994), Zips et al. (2005) recognizes that *in vitro* tumor models continue to be useful and relevant in the analysis of anticancer agents.

The specification includes working examples disclosing the effectiveness of four agents in decreasing PC-3 tumor cell migration. The examples use an *in vitro* model recognized by the skilled person as a useful cell line for *in vitro* screens to identify anticancer agents. Moreover, the PC-3 cell line represents actual specific prostate metastatic tumors; this cell line produces metastatic tumors in mice. The further evaluation of promising anticancer agents using *in vivo* animal models is routine. Moreover, the Examiner is requested to note that enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, screening agents that decrease MscCa channel activity in *in vivo* animal models does not constitute "undue experimentation," particularly in an art where the level of skill is high. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The references cited in the Office Action appear to be included to support the Examiner's position that a high level of unpredictability results in lack of enablement. It is the

applicant's position that the cited art indicates that a great deal of experimentation is routine in this art.

For at least these reasons, the Examiner is respectfully requested to reconsider and withdraw the present rejection of claims 20-23, 26, 27, 29, and 30 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejection

The Examiner rejected claims 20-22 under 35 U.S.C. §102(b) as being anticipated by Evans et al. (U.S. Patent No. 6,214,824) as evidenced by Du et al. (Urology, 2007; 69:590-595). This rejection is respectfully traversed.

Evans et al. discloses methods for suppressing the invasion and spread of cancer cells using amiloride to inhibit the proliferation and invasive capability of epithelial based cancers which are dependent on the plasmin enzymatic cascade. Evans et al., column 1, lines 11-15. Du et al. examines whether mechanosensitive ion channels, including epithelial Na+ channels, are implicated in mechanosensory transduction of the rat urinary bladder. Du et al., page 590, Objectives. The authors conclude that "the amiloride-sensitive ENaC [degenerin/epithelial Na^+ channel] expressed in the bladder epithelium is implicated in the mechanosensory transduction mechanism . . . ." Du et al., sentence bridging pages 594-595. In contrast, independent claims 20, 21, and 22 recite "a mechanosensitive Ca^{2+}-permeable (MscCa) channel." Evans et al. and Du et al. do not teach or suggest a mechanosensitive Ca^{2+}-permeable channel. Since neither Evans et al. nor Du et al. teach a mechanosensitive Ca^{2+}-permeable channel, Evans et al. as evidenced by Du et al. cannot anticipate claims 20-22.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 20, 21, and 22 is respectfully requested.

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581336
Minneapolis, MN 55458-1336
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

April 6, 2009
Date

By: _____
David L. Provence
Reg. No. 43,022
Direct Dial (612) 305-1005

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with 37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to the Commissioner for Patents, Mail Stop **Amendment**, P.O. Box 1450, Alexandria, VA 22313-1450, on this 6th day of April, 2009.

By: _____
Name: Dani Morozs